In the related parent application from which the present application is filed as a continuation application under 37 C.F.R. 1.53(b), Claims 26-30 (have been previously rejected under 35 USC §103(a) as being obvious over Culver et al. (WO 93/21959) in view of Lupton et al. (WO 92/08796). Applicants have addressed these rejections in a Response under 37 C.F.R. §1.116 which was filed on September 1, 2000 in the parent application (Serial No. 08/978,293) but which the Examiner indicated in her Advisory Action (dated September 28, 2000) for the parent application, would not be entered because the claim amendments raise new issues.

In the Advisory Action to the parent application, the Examiner maintains the rejections of claims 26-30 under 35 U.S.C. §103(a) as obvious over Culver et al. in view of Lupton et al. In addition, the Examiner objects to the addition of the term "purified" to claims 22 and 26 alleging that what is meant by purified is vague and unclear. The Examiner states that "purified retroviral vector" could include 75% of the GDV as producer cells.

Although Applicants address the prior rejection in this Preliminary Amendment in order to advance prosecution, the remarks made by Applicants are not to be taken as admission that such a rejection was properly made in the parent application or should be made in this Continuation Application. Rather, these remarks are being made solely in order to advance prosecution and to enable the Examiner to consider the new claims in view of these remarks.

Accordingly, entry of the amendment made to the Continuation Application by way of this Preliminary Amendment and allowance of the claims are respectfully requested.

Rejections under 35 U.S.C.§103(a)

Previously, the Examiner rejected original claims 26-30 under 35 U.S.C. §103(a) as obvious over Culver et al. in view of Lupton et al. The Examiner maintains her rejection that Culver et al. teach a method for *in situ* treatment comprising introducing directly into the tumor a retroviral vector and in a preferred embodiment a second nucleotide, concluding that Culver et al.'s method for *in situ* treatment anticipates the claimed invention.

Applicants respectfully assert that these rejections have been traversed for the following reasons.

First, Applicants respectfully reject the Examiner's assertions that the present invention would be obvious in view of the teachings of Culver et al. On the contrary, after a thorough review of Culver et al., Applicants assert that one skilled in the art would not have known that use of a combination of vectors such as two more retroviral vectors would provide a synergistic effect on tumor regression.

As previously stated and distinctly pointed out in Culver et al., the thrust of the Culver PCT publication is to teach a method for treating a tumor based on a bystander effect. So crucial to the efficacy of Culver's methodology is this bystander effect, that they repeatedly emphasize the importance of this phenomena throughout their entire PCT publication. Indeed, as recited in the first step of their first independent claim, Culver et al.'s method for *in situ* treatment of a tumor comprises "(a) characterizing a tumor as one that exhibits a bystander effect" (see claim 1 at page 25). This is a significant and patentable distinction between Applicants' invention and the cited reference.

For example, Culver et al. starts out their Detailed Description of Preferred Embodiments at page 5, stating:

> 'Notwithstanding previous failed attempts to develop a cancer therapy based on gene transfer, an approach has been discovered for treating cancer effectively by retroviral vector mediated gene transfer *in vivo*. A ***key*** to the success of the new approach is the recognition that certain tumors exhibit a "bystander effect" which had not been identified previously.' (emphasis added)

Nowhere throughout the entire Culver et al. publication is there mention of treating tumors without first selecting for those tumors that have "been determined to exhibit a bystander effect" (Culver et al., page 6, lines 23-24). Indeed, Culver et al. clearly states at page 6, lines 7-8, that "[i]dentifying a tumor as one that displays such a bystander effect is the ***departure point***, pursuant to the present invention," (emphasis added).

The distinction between the subject invention and the cited reference is further underscored by the significant disclosure in Culver et al. directed at teaching methods

for screening and identifying tumors which exhibit a bystander effect so that "transformation and subsequent treatment are ***targ ted*** ...to tumors that exhibit a bystander effect (see Culver et al., page 7, lines 15-17, emphasis added). Indeed, the title of the Culver et al. reference, "Bystander Effect Tumoricidal Therapy", further reflects the overall purpose and entire focus of the subject matter disclosed in the cited reference. Culver et al. never discloses nor suggests Applicants' novel method of treatment comprising administering more than one vector carrying desired nucleic acid molecules for disease treatment. Therefore, Culver et al.'s disclosed method which is dependent on first identifying and selecting for those tumors having a bystander effect, clearly teaches away from Applicants' invention.

Obviousness can only be established where there is some teaching, suggestion or motivation to produce the claimed invention found in the prior art or in the knowledge generally available to one of ordinary skill in the art. *In re Jones*, 958 F.2d 347, 21 U.S.P.Q. 2d 1941 (Fed. Cir. 1992). Hindsight analysis should not be used in determining what would have been obvious to one of ordinary skill in the art at the time the invention was made. *Panduit Corp. v. Dennison Manufacturing Co.,* 1 U.S.P.Q. 2d 1593 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Here, the synergistic effect and efficacy of administering more than one gene delivery vehicle to an animal or patient was not known nor established prior to the present invention. Therefore, Culver et al. does not provide adequate teaching, suggestion or motivation so that one skilled in the art could arrive at the claimed invention.

Recitation of "purified" raises issues of §112, 2nd paragraph

The Examiner indicates in her Advisory Action (dated September 28, 2000 to the parent application) that the recitation of "purified" in the claims as amended raises the issue of §112, 2nd paragraph because the term is not defined specifically in the specification and "since the retroviral vector must be isolated to practice the claimed method" the metes and bounds are not clearly defined. The Examiner further states that although the specification discloses that "GDVs are typically purified to a level ranging from 0.25% to 25%", because this quantitative range "could include 75% of the GDV as producer cells", that the claims remain unpatentable in view of the Culver et al. reference.

Applicants generally agree with the Examiner that a "purified retroviral vector" could include 75% of the GDV as producer cells. However, Applicants point out that purified is a well-accepted term in the field of molecular biology, retrovirology and other sciences. For example, as published in Harcourt's Academic Press Dictionary of Science and Technology, "purify" is defined as "to remove extraneous materials from a substance." Therefore, the term purified is clear and definite as understood in the art. Applicants further direct the Examiner's attention to the specification where the paragraph disclosing the level of purity of the GDVs, when taken in the context of the full paragraph, clearly define what is meant by "purified". For example, at page 48, lines 31 - 36, the specification discloses:

> "The GDVs are typically purified to a level ranging from 0.25% to 25%, and preferably about 5% to 20% before formulation. Subsequently, after preparation of the composition, where the GDV is a recombinant virus, the recombinant virus will constitute about 10 ng to 1 ug of material per dose, with about 10 times this amount of material present as copurified contaminants."

As well known in the molecular biological arts, percentage levels of a substance refer to the amount or quantity of a particular indicated material ***relative*** to the amount of other material(s) present in a particular sample or composition Therefore, "5% to 20%" purity level would comprise 5 percent to 20 percent GDV relative to the total quantity of materials or composition of the sample. Furthermore, although the scope of the claimed compositions encompasses producer cells, Applicants assert that this does not render the claimed invention obvious over the Culver et al. reference. As Applicants have discussed above, Culver et al. clearly teaches away from Applicants' invention, which is not dependent on first identifying and selecting for those tumors having a bystander effect.

The Examiner also states that since the pending claims do not recite that the retroviral vectors must be administered "free of the producer cells", that the claims remain unpatentable in view of the Culver et al. reference. The invention as claimed does not require administration of retroviral vectors that are free of producer cells, but the administered compositions can, if desired, include producer cells. However, Applicants again assert for the reasons stated above, that the claimed invention is not

obvious over the Culver et al. reference because Culver et al. requires identifying and selecting for tumors having a bystander effect, a phenomena not required by the present invention.

Conclusion

In view of the foregoing, it is submitted that all pending claims are now in condition for allowance. Allowance is respectfully requested.

If for any reason direct communication with Applicant's attorney would serve to advance prosecution of this case to finality, the Examiner is invited to call the undersigned attorney at the below listed telephone number.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 16-2230.

Respectfully submitted,

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